SHOTWELL & CARR, INC. SERVING THE FDA/EPA/USDA REGULATED INDUSTRIES SINCE 1974

3535 FIREWHEEL DR., SUITE A, FLOWER MOUND, TX 75028-2628
PHONE (972) 355-9700 FAX (972) 355-9984
E-MAIL: mshepart@shotcarr.com
Web Page: www.shotcarr.com

December 1, 1999

SUITABILITY PETITION

Dockets Management Branch
HFA-305, Room 4-62
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Suitability Petition

Dear Sir/Madam:

Enclosed are four copies of a suitability petition we are filing on behalf of Tyler Group, Inc., St. Louis, MO. The petition requests the Commissioner to permit Tyler Group to file an abbreviated new animal drug application (ANADA) for enalapril maleate tablets having a different dosage form (palatable, chewable tablets) than that of the listed approved new animal drug (Enacard® Tablets, Merial, Ltd., NADA 141-015).

Please do not hesitate to contact us if additional information is required at this time.

Sincerely,

Mark L Shepard

Mark L. Shepard, M.S.
Vice President

Enclosure

Cc: Tyler Group, Inc.

MLS:pbh

H:\users\common\239\suitabilityltr

99P-5330

CP1

TYLER GROUP INC.
11960 Westline Ind. Dr., Suite 180
St. Louis, MO 63146
TEL: (314) 205-9033, FAX: (314) 205-9090
E-MAIL: tgi@tylergroup.com

November 30, 1999

Center for Veterinary Medicine
Food and Drug Administration
Metro Park North Two
7500 Standish Place
Rockville, MD 20855

Dear Sir or Madam:

Please accept this letter as authorization for Shotwell & Carr, Inc., to act on behalf of Tyler Group, Inc., in regard to all matters pertaining to the Food, Drug and Cosmetic Act, as amended.

Sincerely,

William B. Moskoff
President

SUITABILITY PETITION

Petition Filed By:
Tyler Group, Inc.
11960 Westline Drive, Suite 180
St. Louis, Missouri 63146

Proposed Product:
A Palatable, Chewable Tablet Form of Enalapril Maleate

Date: November 30.1999

TYLER GROUP INC.
11960 Westline Ind. Dr., Suite 180
St. Louis, MO 63146
TEL: (314) 205-9033, FAX: (314) 205-9090
E-MAIL: tgi@tylergroup.com

SUITABILITY PETITION

The undersigned submits this petition under 5 12(n)(3) of the Federal Food, Drug, and Cosmetic Act, to request the Commissioner of Food and Drugs to allow the filing of an abbreviated new animal drug application whose dosage form differs from that of the approved new animal drug.

Name: William B. Mosbaugh

Title: President

11/30/99
(Date)

I. Action Requested

The requested action is for the Commissioner to permit the filing of an abbreviated new animal drug application (ANADA) for our proposed product which differs from the approved pioneer product as follows:

Pioneer Product (Reference Drug)

Enacard® (enalapril maleate), NADA 141-015, approved by the Center for Veterinary Medicine on February 24, 1994, sponsored by Merial Ltd., is an immediate release tablet indicated for use for the treatment of mild, moderate and severe (modified New York Heart Association Class II, III, IV) heart failure in dogs. It is offered in five tablet strengths containing 1.0 mg, 2.5 mg, and 5.0 mg, 10.0 mg and 20 mg of enalapril maleate.

Proposed Product

The proposed product is a palatable, chewable tablet form containing 5.0 mg enalapril maleate, which will be indicated for use in dogs for the same claim(s) and will utilize the same oral dosage regime as the pioneer product.

II. Statement of Grounds

Disease states for which enalapril is prescribed frequently require long term administration of the drug on an established programmed dosage schedule.

This schedule may require as much as twice daily administration. It is sometimes extremely difficult to administer oral solid dosage forms to dogs due to their reluctance to accept and swallow the medication. Thus, even though the drug may be properly prescribed, if the pet owner meets resistance in administering the drug then doses may be missed and the animal will receive insufficient medication. The approval of this petition and the ultimate approval of a generic animal drug application for a palatable, chewable tablet form of enalapril would provide the pet owner with an alternative product which is more readily administered and accepted. Hence, the pet owner is more likely to be able to assure the animal is receiving the proper dose of medication as prescribed by the veterinarian for the animal's particular disease state.

The legal basis under which this application proceeds is as promulgated in the FD&C Act which allows the Commissioner to accept a generic drug application for an animal drug product which differs in dosage form from the pioneer or reference drug product. The dosage form for the proposed generic product described in this petition is similar to that of the pioneer drug in that both products are oral tablets, and both are immediate release dosage forms. The only real difference is that this proposed generic product is in a palatable, chewable form.

The petitioner is not aware of any information which would be unfavorable to the granting of the requested action.

III. Environmental Impact

The Tyler Group, Inc., hereby requests a categorical exclusion from the requirements of preparing an environmental assessment based on 21 CFR 25.30(h). This subparagraph provides for categorical exclusions for actions such as the issuance, amendment, or revocation of procedural or administrative regulations and guidelines, including procedures for submission of applications for product development, testing and investigational use, and approval. To the best of petitioner's knowledge, no extraordinary circumstances exist which may significantly affect the human environment as discussed under 21 CFR 25.21.

IV. Economic Impact

An economic impact statement pertaining to (1) Cost (and price) increases to industry, government, and consumers; (2) productivity of wage earners, businesses, or government; (3) competition; (4) supplies of important materials, products, or services; (5) employment; and (6) energy supply or demand has not been prepared for this petition. Tyler Group, Inc., will provide such an analysis if so requested by the Commissioner.

V. Identification of Single Listed Pioneer Drug

NADA NO.	NAME OF DRUG	COMPANY	APPROVAL DATE
141-015	Enacard®	Merial Ltd.	02/24/1994

VI. Labeling

The following pages provide copies of the proposed generic product labeling and the reference drug labeling.

Differences between the proposed generic product labeling and the pioneer product labeling:

1. Changed " ENACARD" to [Tyler Brand Name] throughout.
2. Added descriptor in several places that tablets are palatable and chewable.
3. Removed references in the package insert which pertain to clinical studies performed by the pioneer sponsor.
4. Added the following statement as the final paragraph under "Precautions":

   "Due to the palatable nature of [Tyler Brand Name], store out of reach of pets in a secured location. Severe adverse reactions may occur if large quantities of tablets are ingested." This statement is also added to the side panel of the bottle label.

5. Added the following statement as the first paragraph under "Dosage and Administration":

"[Tyler Brand Name] tablets are palatable and willingly consumed by most dogs when offered by the owner. Therefore, they may be fed by hand or placed on food. Care should be taken to assure that the pet has consumed the complete dose."

6. Removed "Safety" section.

7. Changed signature blocks to reflect appropriate company name for the proposed product.

VII. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to this petition.

Signature: Mark A Shepard

Name of Petitioner: Tyler Group, Inc.

Mailing Address: 11960 Westline Industrial Drive, Ste. 180
St. Louis, MO 63146

Telephone Number: (314) 2059033

PROPOSED LABELING

Front Panel

[TYLER BRAND NAME]
(Enalapril Maleate)

5.0 mg.

Chewable, Palatable Tablet
For Dogs

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian

Net Contents: xx Chewable Tablets

NADA No. xxx-xxx, Approved by FDA

Manufactured for:

TYLER GROUP, INC.
ST. LOUIS, MO 63146

Side Panel

PROTECT FROM MOISTURE

INDICATIONS: Treatment of mild, moderate, and severe (modified New York Heart Association Class II, Ill, IV) heart failure in dogs.

CAUTION: Due to the palatable nature of [TYLER BRAND NAME], store out of reach of pets in a secured location. Severe adverse reactions may occur if large quantities of tablets are ingested.

See Package Insert for Complete Indications and Use Directions

Store below 30" (86°C) and avoid transient temperature above 50°C (122°F). Keep container tightly closed. Do not remove desiccant.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN

Lot No. _____ Exp. Date: _____

"[TYLER BRAND NAME]" Prescribing information

TABLETS FOR HEART FAILURE IN DOGS

CAUTION

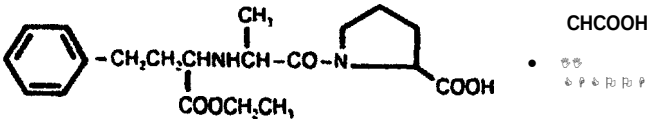
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

[Tyler Brand Name] contains the maleate salt of enalapril, a derivative of two amino-acids, L-alanine and L-proline. Following oral administration, enalapril (a prodrug) is rapidly absorbed and then hydrolyzed to enalaprilat, which is a highly specific, long-acting. non-sulfhydryl angiotensin converting enzyme (ACE) inhibitor. ACE is a dipeptidase that catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor which stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II levels, which leads to decreased vasopressor activity and to decreased aldosterone secretion. ACE inhibitors are neurohormonal antagonists that are balanced (both arterial and venous) vasodilators resulting in decreased preload and afterload. The overall effect of enalapril treatment is a decrease in the workload of the heart resulting from both arterial and venous dilation and decreased fluid retention.

CHEMISTRY

[TYLER BRAND NAME] tablets contain the maleate salt of enalapril, the ethyl ester of the parent diacid, enalaprilat. Enalapril maleate is chemically described as (S)-1(N-(1-(ethoxycarbonyl)-3-phenylpropyl)-L-alanyl)-L-proline,
(Z)-2-butenedioate sale (1 :1). The empirical formula is $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$, and the structural formula is:



INDICATIONS

[Tyler Brand Name] is indicated for the treatment of mild, moderate, or severe (modified NYHA Class II^a, III^b, IV^c) heart failure in dogs. (See CASE MANAGEMENT section for etiologies and appropriate conjunctive therapies.)

[a] A dog with modified New York Heart Association Class II heart failure develops fatigue, shortness of breath, coughing, etc., which becomes evident when ordinary exercise is exceeded.

[b] A dog with modified New York Heart Association Class III heart failure is comfortable at rest, but exercise capacity is minimal.

[c] A dog with modified New York Heart Association Class IV heart failure has no capacity for exercise and disabling clinical signs are present at rest.

DOSAGE AND ADMINISTRATION

The recommended starting dose of [Tyler Brand Name] in dogs is 0.5 mg/kg administered orally s.i.d. (once daily) with or without food. In the absence of an adequate clinical response within 2 weeks, the dosing frequency may be increased to b.i.d. (twice daily) for a total daily dose of 1 mg/kg. The clinical response should be evaluated based on criteria that include a physical exam, degree of pulmonary congestion/edema demonstrated on chest radiographs, the level of activity displayed by the dog, and exercise tolerance. This dose increase may be initiated earlier if indicated by worsening signs of heart failure such as increased pulmonary congestion/edema, decreased level of activity or decreased exercise tolerance. Dogs should be observed closely for 48 hours following initial dosing or after increasing the dosing frequency for clinical signs consistent with hypertension such as weakness or depression. In addition, renal function should be monitored closely both before and 2 to 7 days after starting treatment with [Tyler Brand Name].

Dogs should be receiving standard heart failure therapy including stable doses of furosemide, with or without digoxin. Dogs should be receiving **a** stable dose of furosemide for at least two days before treatment with [Tyler Brand Name] and, if included in the treatment regimen, a stable dose of digoxin should be administered for four days prior to initiation of therapy with [Tyler Brand Name].

In the event that clinical signs of hypertension or reduced kidney function occur or that a significant increase in the concentration of blood urea nitrogen (BUN) and/or serum creatinine (CRT) over pretreatment levels is detected, refer to the PRECAUTIONS section for appropriate response.

[Tyler Brand Name] tablets are palatable and willingly consumed by most dogs when offered by the owner. Therefore, they may be fed by hand or placed on food. Care should be taken to assure that the pet has consumed the complete dose.

[Tyler Brand Name] is available in 5 mg tablet strength.

CASE MANAGEMENT

Because of the treatment of dogs with heart failure, it may be necessary to consult with a veterinary cardiologist or internist.

[Tyler Brand Name] is indicated for the treatment of dogs in heart failure due to mitral regurgitation (chronic valvular disease) and/or reduced ventricular contractility (dilated cardiomyopathy). Conjunctive therapy which should be used with [Tyler Brand Name] consists of furosemide and digoxin in the treatment of dilated cardiomyopathy, and furosemide with or without digoxin in the treatment of chronic valvular disease. [Tyler Brand Name] acts to ameliorate the clinical signs associated with heart failure rather than to reverse the degeneration of the atrioventricular valves or to resolve the underlying myocardial disease in dilated cardiomyopathy. Efficacy against heart failure caused by etiologies other than mitral regurgitation or dilated cardiomyopathy has not been demonstrated.

DIAGNOSIS AND MONITORING

As the heart failure disease syndrome is complex and usually requires multiple therapies, it is important to establish an accurate diagnosis. Diagnosis is based on procedures such as a complete physical examination, auscultation, electrocardiography, radiography, echocardiography, and pertinent laboratory tests, including hematology, clinical chemistry and urinalysis. Dogs should be evaluated by assessing the class of heart failure, severity of pulmonary edema, appetite, level of activity, mobility, and cough prior to initiating treatment and again two (14 days) and four (28 days) weeks after starting treatment. Client observations are important in the successful monitoring of treatment. During long-term therapy, dogs should be evaluated approximately every three months unless conditions require that individual dogs be monitored more frequently. For dogs receiving digoxin therapy serum digoxin concentrations should also be measured at these times or if indicated by inappetence, vomiting or diarrhea.

In addition, pertinent laboratory tests, including hematology and clinical chemistry, are to be performed with attention to monitoring BUN and CRT concentrations.

CONCOMITANT THERAPY

[Tyler Brand Name] may be used concomitantly with other therapy, which may include furosemide, digoxin, antiarrhythmics, beta-blockers, bronchodilators and cough suppressants for the treatment of heart failure in dogs. [Tyler Brand Name] may be used in combination with sodium-restricted diets. The safety of [Tyler Brand Name] when used concomitantly with other cardiovascular drugs (e.g., vasodilators) has not been established.

PRECAUTIONS

Renal Functions

The use of diuretics is considered an important part of therapy for heart failure. The result is that some dogs are kept in a volume-depleted (slightly dehydrated) state to control their heart failure. If cardiac function is impaired, the relative volume of blood reaching the kidneys is decreased, leading to pre-renal azotemia. The renal flow, already impaired by heart failure, is further compromised by volume depletion. Pre-renal azotemia is exacerbated. In normal dogs, pre-renal azotemia is confirmed by examination of urine specific gravity; however, administration of diuretics renders this diagnostic test invalid.

Clinical manifestations of the heart failure syndrome may include pre-renal azotemia, which is defined as an elevation in BUN and/or CRT with a normal urinalysis. This usually results from decreased renal blood flow induced by impaired cardiovascular performance. Compounds that cause volume depletion, such as diuretics or angiotensin converting enzyme inhibitors, may lower systemic blood pressure, which may further decrease renal perfusion and lead to the development of azotemia. Dogs with no detectable renal disease may develop minor and transient increases in BUN or CRT when [Tyler Brand Name] is administered concomitantly with furosemide.

1. If clinical signs of hypertension or signs of azotemia develop, the dose of furosemide should be reduced first.
2. If signs of azotemia continue it may be necessary to further reduce the daily dose of furosemide or discontinue administration.
3. If there is still no improvement in clinical signs, dosing with [Tyler Brand Name] should be decreased in frequency to once daily if being given twice daily, or discontinued.
4. Renal function (BUN and CRT) should be monitored periodically until it returns to pretreatment levels.
5. Appropriate fluid therapy, carefully monitored, should be considered if the above steps do not reverse azotemia.

Due to the palatable nature of [Tyler Brand Name], store out of reach of pets in a secured location. Severe adverse reactions may occur if large quantities of tablets are ingested.

USE IN BREEDING ANIMALS

Safety of enalapril in breeding dogs has not been established. Use of enalapril in pregnant bitches is not recommended.

Keep this and all drugs out of the reach of children.
In case of ingestion by humans, clients should be advised to contact a physician immediately.

ADVERSE REACTIONS

Enalapril is generally well tolerated in dogs. If adverse effects associated with azotemia are observed, refer to the PRECAUTIONS section for recommended action.

Azotemia

Azotemia may be based on the veterinarian's medical opinion (clinical signs or laboratory values) or defined as a BUN value of ≥50 mg/dL and/or a CRT value of ≥2.5 mg/dL, since dogs in heart failure and dogs receiving furosemide have higher values than normal dogs.

Other Clinical Observations/Adverse Reactions

Some clinical observations may be attributable to treatment with furosemide and digoxin, and to the disease process itself. These include polyuria and polydipsia, depression, lethargy, 'anorexia, and decreased activity. Vomiting and other signs associated with the gastrointestinal tract may be seen as a result of cardiac glycoside toxicity when digoxin is administered in conjunction with furosemide or furosemide and enalapril.

STORAGE

Protect from moisture. Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F). When not in use keep container tightly closed. Do not remove desiccant from the container. Subdivision of the product package is not recommended, as the product should be stored in an airtight container.

HOW SUPPLIED

Tablet are supplied in bottles containing xx tablets (with desiccant).

Manufactured for:
Tyler Group, Inc.
11960 Westline Drive
St. Louis, MO 63146

1199
Made in USA

REFERENCE DRUG LABEL

MERCK
83545/120594
Enacard® 5mg
(enalapril maleate)
Tablets for Dogs
30 Tablets/5.0mg each
CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.
Merck AgVet Division, Merck & Co., Inc.,
PROTECT FROM MOISTURE. Store below 30°C (86°F) and avoid transient temperature above 50°C (122°F). Keep container tightly closed. Do not remove desiccant.
U.S. Pat. 4,374, 829.
Made in the U.K.
ENACARD is a registered trademark of Merck & Co., Inc., Whitehouse Station, N.J., U.S.A.
See Package Outsert Accompanying This Bottle For Complete Indications and Use Directions.
Keep this and all drugs out of the reach of children.
Lot No.: 990260
Exp: NOV 00

ENACARD®
(enalapril maleate)

TABLETS for HEART FAILURE in DOGS

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: ENACARD contains the maleate salt of enalapril, a derivative of two amino-acids, L-alanine and L-proline. Following oral administration, enalapril (a prodrug) is rapidly absorbed and then hydrolyzed to enalaprilat, which is a highly specific, long-acting, non-sulfhydryl angiotensin converting enzyme (ACE) inhibitor. ACE is a dipeptidase that catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor which stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II levels, which leads to decreased vasopressor activity and to decreased aldosterone secretion. ACE inhibitors are neurohormonal antagonists that are balanced (both arterial and venous) vasodilators resulting in decreased preload and afterload. The overall effect of enalapril treatment is a decrease in the workload of the heart resulting from both arterial and venous dilation and decreased fluid retention.

INDICATIONS: ENACARD is indicated for the treatment of mild, moderate, or severe (modified NYHA Class II(a), III(b), IV(c)) heart failure in dogs. (See CASE MANAGEMENT section for etiologies and appropriate conjunctive therapies.)

(a) A dog with modified New York Heart Association Class II heart failure develops fatigue, shortness of breath, coughing, etc., which becomes evident when ordinary exercise is exceeded.
(b) A dog with modified New York Heart Association Class III heart failure is comfortable at rest, but exercise capacity is minimal.
(c) A dog with modified New York Heart Association Class IV heart failure has no capacity for exercise and disabling clinical signs are present at rest.

DOSAGE AND ADMINISTRATION: The recommended starting dose of ENACARD in dogs is 0.5 mg/kg administered orally s.i.d. (once daily) with or without food. In the absence of an adequate clinical response within 2 weeks, the dosing frequency may be increased to b.i.d. (twice daily) for a total daily dose of 1 mg/kg. The clinical response should be evaluated based on criteria that include a physical exam, degree of pulmonary congestion/edema demonstrated on chest radiographs, the level of activity displayed by the dog, and exercise tolerance. This dose increase may be initiated earlier if indicated by worsening signs of heart failure such as increased pulmonary congestion/edema, decreased level of activity or decreased exercise tolerance. Dogs should be observed closely for 48 hours following initial dosing or after increasing the dosing frequency for clinical signs consistent with hypotension such as weakness or depression. In addition, renal function should be monitored closely both before and 2 to 7 days after starting treatment with ENACARD.

Dogs should be receiving standard heart failure therapy including stable doses of furosemide, with or without digoxin. Dogs should be receiving a stable dose of furosemide for at least two days before treatment with ENACARD and, if included in the treatment regimen, a stable dose of digoxin should be administered for four days prior to initiation of therapy with ENACARD.

In the event that clinical signs of hypotension or reduced kidney function occur or that a significant increase in the concentration of blood urea nitrogen (BUN) and/or serum creatinine (CRT) over pretreatment levels is detected, refer to the PRECAUTIONS section for appropriate response.

In the clinical studies, dogs with dilated cardiomyopathy generally responded more rapidly than dogs with mitral regurgitation as noted by the higher percentages of dogs demonstrating improved scores on Day 14 for class of heart failure, overall evaluation, mobility, attitude and activity. On Day 28, dogs with dilated cardiomyopathy responded better than dogs with mitral regurgitation as demonstrated by higher percentages of dogs showing improvement for class of heart failure, overall evaluation, mobility, attitude and activity.

ENACARD is available in 5 tablet strengths:

Tablet Strength	Tablet Color	Product No.
1.0 mg	Green	48501
2.5 mg	Blue	48502
5.0 mg	Pink	48505
10.0 mg	Yellow	48510
20.0 mg	White	48520

CASE MANAGEMENT: Because of the complexity of the treatment of dogs with heart failure, it may be necessary to consult with a veterinary cardiologist or internist.

ENACARD is indicated for the treatment of dogs in heart failure due to mitral regurgitation (chronic valvular disease) and/or reduced ventricular contractility (dilated cardiomyopathy). Conjunctive therapy which should be used with ENACARD consists of furosemide and digoxin in the treatment of dilated cardiomyopathy, and furosemide with or without digoxin in the treatment of chronic valvular disease. ENACARD acts to ameliorate the clinical signs associated with heart failure rather than to reverse the degeneration of the atrioventricular valves or to resolve the underlying myocardial disease in dilated cardiomyopathy. Efficacy against heart failure caused by etiologies other than mitral regurgitation or dilated cardiomyopathy has not been demonstrated.

Diagnosis and Monitoring: *As the heart failure disease syndrome is complex and usually requires multiple therapies, it is important to establish an accurate diagnosis.* Diagnosis is based on procedures such as a complete physical examination, auscultation, electrocardiography, radiography, echocardiography, and pertinent laboratory tests, including hematology, clinical chemistry and urinalysis. In clinical studies, dogs were evaluated by assessing the class of heart failure, severity of pulmonary edema, appetite, level of activity, mobility, and cough prior to initiating treatment and again two (14 days) and four (28 days) weeks after starting treatment (See EFFICACY section). Client observations are important in the successful monitoring of treatment. During long-term therapy, dogs were evaluated approximately every three months unless conditions required that individual dogs be monitored more frequently. For dogs receiving digoxin therapy, serum digoxin concentrations were also measured at these times or if indicated by inappetence, vomiting or diarrhea.

In addition, pertinent laboratory tests, including hematology and clinical chemistry were performed with attention to monitoring BUN and CRT concentrations.

STABILITY: *ENACARD tablets have been shown to be stable for 24 months at room temperature.*

CONCOMITANT THERAPY: As established during clinical studies, ENACARD may be used concomitantly with other therapy, which may include furosemide, digoxin, antiarrhythmics, beta-blockers, bronchodilators and cough suppressants, for the treatment of heart failure in dogs. ENACARD may be used in combination with sodium-restricted diets. The safety of ENACARD when used concomitantly with other cardiovascular drugs (e.g., vasodilators) has not been established.

PRECAUTIONS: *Renal Function:* *The use of diuretics is considered an important part of therapy for heart failure.* The result is that some dogs are kept in a volume-depleted (slightly dehydrated) state to control their heart failure. If cardiac function is impaired, the relative volume of blood reaching the kidneys is decreased, leading to pre-renal azotemia. If the renal flow, already impaired by heart failure, is further compromised by volume depletion, pre-renal azotemia is exacerbated. In normal dogs, pre-renal azotemia is confirmed by examination of urine specific gravity; however, administration of diuretics renders this diagnostic test invalid. In clinical trials, the pre-treatment serum chemistry profiles showed that the mean BUN was *28.7 mg/dL and the mean serum CRT was 1.27 mg/dL, indicating that dogs in heart failure receiving* furosemide therapy may have elevations in BUN and CRT.

Clinical manifestations of the heart failure syndrome may include pre-renal azotemia, which is defined as an elevation in BUN and/or CRT with a normal urinalysis. This usually results from decreased renal blood flow induced by impaired cardiovascular performance. Compounds that cause volume depletion, such as diuretics or angiotensin converting enzyme inhibitors, may lower systemic blood pressure, which may further decrease renal perfusion and lead to the development of azotemia. Dogs with no detectable renal disease may develop minor and transient increases in BUN or CRT when ENACARD is administered concomitantly with a furosemide.

1. If clinical signs of hypotension or signs of azotemia develop, the dose of furosemide should be reduced first.
2. If signs of azotemia continue, it may be necessary to further reduce the daily dose of the furosemide or discontinue administration.
3. If there is still no improvement in clinical signs, dosing with ENACARD should be decreased in frequency to once daily if being given twice daily, or discontinued.
4. Renal function (BUN and CRT) should be monitored periodically until it returns to pretreatment levels.
5. Appropriate fluid therapy, carefully monitored, should be considered if the above steps do not reverse azotemia.

Use in Breeding Animals: Safety of enalapril in breeding dogs has not been established. Use of enalapril in *pregnant bitches is not recommended.*

Keep this and all drugs out of the reach of children.

In case of ingestion by humans, clients should be advised to contact a physician immediately.

ADVERSE REACTIONS: ENACARD has been demonstrated to be generally well tolerated in controlled, open-label field and clinical laboratory studies that involved *414 dogs with mild, moderate, or severe heart* failure. In clinical studies, the overall prevalence of adverse effects was no greater in dogs treated with standard therapy (furosemide with or without digoxin) and ENACARD than in those treated with standard therapy and placebo. Since three therapies (enalapril, furosemide, and digoxin) were used in conjunctive therapy, adverse reactions were difficult to associate with a particular drug. If adverse effects associated with azotemia are observed, refer to the PRECAUTIONS section for recommended action.

Azotemia: In clinical studies, azotemia was based on the clinical investigator's medical opinion (clinical signs or laboratory values) or defined as a BUN value of ≥50 mg/dL and/or a CRT value of ≥2.5 mg/dL, since dogs in heart failure and dogs receiving a diuretic have higher values than normal dogs.

There was no significant difference in the prevalence of azotemia in dogs receiving standard therapy and placebo compared with those receiving standard therapy and ENACARD. Of 381 dogs in clinical field studies, azotemia as defined above was reported in 25.9% of 116 dogs receiving standard therapy and placebo, and in 28.7% of 265 dogs receiving standard therapy and enalapril. Azotemia was the cause of discontinuation of therapy in 4.3% of the dogs receiving standard therapy and placebo and of 3.0% of the dogs receiving standard therapy and ENACARD in these clinical studies.

Other Clinical Observations/Adverse Reactions: Some clinical observations are attributable to treatment with furosemide and digoxin and to the disease process itself. These include polyuria and polydipsia, depression, lethargy, anorexia, and decreased activity. Vomiting and other signs associated with the gastrointestinal tract may be seen as a result of cardiac glycoside toxicity when digoxin is administered in conjunction with furosemide or furosemide and ENACARD.

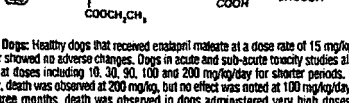
No statistically significant differences in the prevalence of clinical signs were reported between dogs given standard therapy and placebo and those given standard therapy and ENACARD. Clinical observations/adverse reactions reported in field clinical studies are tabulated as follows.

Prevalence of clinical observations/adverse reactions reported in controlled and open-label field clinical studies involving 381 dogs that were treated for up to 15.5 months:

Observations		ENACARD % of dogs N = 265	Placebo % of dogs N = 116
Death:	Total	6.4	10.3
	Heart Failure	1.9	7.8
	Sudden	2.6	1.7
	Other	1.9	0.9
Gastrointestinal:	Anorexia or inappetence	16.9	25.0
	Vomiting, emesis, gastritis, or gastroenteritis, gastric dilation or upset stomach	17.7	17.2
	Diarrhea, loose feces, bloody feces or soft feces	15.5	17.2
Circulatory:	Hemoptysis	0.0	0.9
	Hypotension	1.1	0.0
	Collapse	3.4	4.3
	Syncope	5.3	3.4
	Arrhythmia, atrial fibrillation, cardiac arrest, or ventricular tachycardia	1.1	2.6
	Pleural effusion	0.4	0.9
General:	Lethargy, depression, listlessness, decreased activity, or sluggishness	12.1	20.7
	Trembling, shaking	1.9	0.0
	Weakness, ataxia, immobility, weak hind limb, drowsiness, incoordination or disorientation	7.5	5.2
	Dehydration, electrolyte imbalance or hyperkalemia	2.6	0.9
	Polyuria, polydipsia	0.0	0.9
	Pyrexia	0.4	2.6
	Restlessness, anxiety	0.8	0.9
	Weight loss	1.1	0.9
Renal:	Azotemia (clinical signs or BUN ≥50 mg/dL or CRT ≥2.5 mg/dL)	28.7	25.9
	Azotemia - Adverse Reaction*	3.0	4.3
	Renal Failure	0.4	0.0

* Removed from study

CHEMISTRY: ENACARD tablets contain the maleate salt of enalapril, the ethyl ester of the parent diacid, enalaprilat. Enalapril maleate is chemically described as (S)-1(N-(1-(ethoxycarbonyl)-3-phenylpropyl)-L-alanyl)-L-proline, (Z)-2-butenedioate salt (1:1). The empirical formula is $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$, and the structural formula is:



SAFETY: Healthy Dogs: Healthy dogs that received enalapril maleate at a dose rate of 15 mg/kg/day (15X) for up to one year showed no adverse changes. Dogs in acute and sub-acute toxicity studies also received enalapril maleate at doses including 10, 30, 90, 100 and 200 mg/kg/day for shorter periods. In an acute oral toxicity study, death was observed at 200 mg/kg, but no effect was noted at 100 mg/kg/day. In studies lasting one to three months, death was observed in dogs administered very high doses of 30 and 90 mg/kg/day. Signs observed in these dogs consisted of emesis, anorexia, weight loss, decreased activity, dehydration and tremors. At the highest dose of 90 mg/kg/day, nephrosis, characterized by tubular cell necrosis, tubular casts, crystals and mineralization, tubular cell cytoplasmic vacuolation and diffusely distributed lipids in the tubular cells, was observed. Secondary changes consisted of increased BUN and serum potassium with decreased serum chloride. No drug-induced changes were seen on electrocardiograms.

Dogs in heart failure: *The safety of enalapril maleate was demonstrated in clinical trials when administered* at the recommended dose level to dogs in heart failure. In these studies, clinical observations/adverse reactions were reported with similar frequency in both treatment groups (enalapril treated and placebo controls). (See OTHER CLINICAL OBSERVATIONS/ADVERSE REACTIONS section.)

EFFICACY: Results of the clinical studies demonstrate that treatment with ENACARD results in improved exercise tolerance and increased survival time with improved quality of life in dogs with mild, moderate, or severe (modified NYHA Class II, III, IV) heart failure.

Efficacy of enalapril tablets was confirmed in studies that included 414 dogs with heart failure due to volume overload caused by chronic valvular disease (mitral regurgitation) or reduced ventricular contractility caused by dilated cardiomyopathy. Efficacy of enalapril was evaluated prior to, during, and following completion of treatment in all studies. Evaluations included physical examination, assessment of clinical variables (class of heart failure, pulmonary edema, activity, attitude, mobility, coughing frequency and appetite), electrocardiographic, hemodynamic (mean blood pressure, pulmonary capillary wedge pressure, cardiac output, pulmonary artery pressure, stroke volume, systemic vascular resistance), echocardiographic (pre-ejection period, left ventricular ejection time, fractional shortening, end diastolic diameter, end systolic diameter, velocity of circumferential fiber shortening) and radiographic examinations, as well as complete blood counts, serum chemistry profiles, urinalyses and serum digoxin concentrations. During these studies furosemide and digoxin dose levels were generally within label directions for each drug when used prior to treatment with enalapril. Following the addition of enalapril, in some cases dosages were increased or decreased beyond label direction as clinical signs indicated.

i. Dose Selection Studies: Two controlled-dose selection studies were conducted using 15 dogs with induced heart failure. Heart failure was induced by surgically removing a section of the mitral valve 1 to 5 months prior to testing ENACARD. Pulmonary capillary wedge pressure was selected as the primary indicator of efficacy because elevated wedge pressure (≥10 mmHg) is the major cause of pulmonary congestion and edema in dogs with heart failure. A single oral dose of 0.5 mg/kg of ENACARD significantly ($p<0.05$) decreased mean pulmonary wedge pressure at 8 hours and over the first 24 hours following dosing compared to 0.25 mg/kg. A dose of 0.75 mg/kg did not provide additional benefit over that evident at 0.5 mg/kg.

ii. Dose Confirmation Study: A double-blind study was conducted at 6 sites and included 47 dogs of various breeds, aged 2.5 to 15 years and weighing 3.2 to 64.1 kg. All dogs received standard therapy [furosemide (range of 1.37–10.91 mg/kg/day) with or without digoxin (range of 4.50–25.00 mcg/kg/day)] for heart failure in addition to the test drug. Dogs were treated with either placebo or enalapril tablets at approximately 0.5 mg/kg b.i.d. (range 0.373-0.646 mg/kg) for approximately 21 days. Over the first 24-hour period after initiation of treatment, improvement of several hemodynamic variables was observed in the enalapril group. Relative to baseline, mean pulmonary capillary wedge pressure was significantly ($p<0.05$) decreased 8 hours after starting treatment, heart rate decreased significantly ($p<0.01$) at 4 hours and over the first 24 hours following initiation of treatment, and scores for class of heart failure and pulmonary edema improved significantly ($p<0.05$) after three weeks of treatment in the enalapril group compared to the placebo group.

iii. Short-Term Efficacy Study: A double-blind study was conducted at 19 sites and included 190 dogs with moderate and severe heart failure. Dogs of various breeds, aged 2.5 to 17 years and weighing 2.4 to 68.5 kg were included in the study. All dogs received standard therapy for heart failure [furosemide (range of 0.70–10.54 mg/kg/day) with or without digoxin (range of 2.03–43.86 mcg/kg/day)] in addition to the test drug. Dogs were treated with either placebo or enalapril tablets at approximately 0.5 mg/kg s.i.d. or b.i.d. (range of 0.383-0.723 mg/kg) for approximately 28 days. Treatment was administered s.i.d. for approximately the first 14 days, after which the investigator had the option of increasing the dose to b.i.d. or maintaining the dose s.i.d. for the remaining 14 days.

Significantly ($p<0.05$) more dogs in the placebo group were removed from the study because of an increasing degree of heart failure or death compared to the enalapril group. Two and four weeks after starting treatment, dogs in the enalapril group demonstrated significant ($p<0.05$) improvement relative to baseline in class of heart failure, pulmonary edema score, mobility, overall evaluation, attitude, and activity compared to dogs in the placebo group. During the four-week study, 5 dogs died due to progression of the heart failure in the placebo group whereas none died of heart failure in the enalapril group.

iv. Open-Label Field Efficacy Study: This study was conducted at 17 sites and included 144 dogs with mild, moderate, or severe (modified NYHA Class II, III or IV) heart failure. Dogs of various breeds, aged 1.5 to 18 years and weighing 1.9 to 61.0 kg were included in the study. ENACARD tablets were administered orally s.i.d. or b.i.d. at approximately 0.5 mg/kg (range of 0.225-0.716 mg/kg) for approximately 28 days. All except 11 dogs received standard therapy for heart failure [furosemide (range of 0.52–11.80 mg/kg/day) with or without digoxin (range of 2.42–27.12 mcg/kg/day)]. All scored clinical variables, including class of heart failure, pulmonary edema, activity, mobility, attitude, total cough, appetite, and overall evaluation, showed significant ($p<0.01$) improvement from baseline two and four weeks after starting treatment.

v. Long-Term Efficacy Study: A multicenter study was performed to determine the long-term efficacy of ENACARD and survival in dogs with moderate and severe heart failure. This study was conducted at 14 sites and included 94 dogs. All dogs received placebo or enalapril tablets at approximately 0.5 mg/kg s.i.d. or b.i.d. (range of 0.363-0.738 mg/kg). In addition, all dogs received standard therapy for heart failure that included [furosemide (range of 1.28–8.67 mg/kg/day) with or without digoxin (range of 2.06–26.04 mcg/kg/day)]. Dogs were evaluated periodically for up to 15.5 months. The primary endpoint in the study was death or removal from the study due to an increase in the degree of heart failure, necessitating unblinding of treatment. Survival was significantly ($p<0.05$) longer in the enalapril group (165.3 days) compared to the placebo group (86.1 days).

vi. Exercise Tolerance and Survival Study: A laboratory study was conducted to determine the effect of ENACARD on exercise tolerance and survival in 18 dogs with surgically induced heart failure. Heart failure was induced by surgically removing a section of the mitral valve 1 to 5 months prior to testing ENACARD. Efficacy was assessed by exercising dogs on a treadmill at intervals up to 80 days as well as measuring survival over a period of approximately 1 year. Dogs were treated orally with either enalapril at approximately 0.5 mg/kg or an equivalent placebo tablet. Treatment was administered s.i.d. for the first 10 days and b.i.d. thereafter for the remainder of the study. *During the entire study no other cardiovascular therapy was administered.*

After 80 days of therapy the dogs in the enalapril group ran significantly ($p<0.01$) longer than the dogs in the placebo group. The mean running time was 5.8 minutes in the placebo group and 16.4 minutes in the enalapril group. All dogs in the enalapril group ran longer than they did prior to starting treatment, whereas none of the dogs in the placebo group ran longer than they did prior to starting treatment. In the placebo group, 2 out of 9 (22.2%) dogs survived 357 days compared to 6 out of 9 (66.7%) dogs in the enalapril group over the same period. The study results demonstrated that dogs treated with enalapril had improved exercise tolerance and survived longer relative to controls.

RESULTS OF CLINICAL STUDIES

Study / Clinical Parameters	ENACARD All	ENACARD MR[a]	ENACARD DCM[b]	Placebo All	Placebo MR	Placebo DCM
i. Dose Selection						
PCWP (mmHg)[1] Study 1: 0.25 mg/kg	-0.82	-	-	0.22	-	-
0.50 mg/kg	-6.73	-	-	0.22	-	-
Study 2: 0.50 mg/kg	-1.77	-	-	-0.33	-	-
0.75 mg/kg	-4.33	-	-	-0.33	-	-
ii. Dose Confirmation						
PCWP (mmHg)[1]	-3.22	-1.35	-4.55	0.95	6.0	-1.57
Heart Rate (beats/min)[2]	-10.0	-5.6	-12.9	6.9	12.3	4.1
Class of heart failure[3]	50.0	37.5	57.1	16.7	0.0	23.1
Pulmonary edema[3]	50.0	62.5	42.9	16.7	40.0	7.7
Overall evaluation[3]	63.6	50.0	71.4	27.8	40.0	23.1
iii. Short-term Efficacy						
Class of heart failure[4]	74.7	67.8	89.3	44.8	45.9	42.3
Pulmonary edema[4]	43.0	42.4	44.4	31.0	32.8	25.9
Overall evaluation[4]	77.0	72.9	85.7	40.2	44.3	30.8
iv. Open-Label						
Class of heart failure[4]	69.8	72.0	57.1	-	-	-
Pulmonary edema[4]	42.0	39.8	55.0	-	-	-
Overall evaluation[4]	85.6	88.1	71.4	-	-	-
v. Long-term Study						
Survival (Days to death/failure)	165.3	180.0	141.0	86.1	93.7	66.7
vi. Exercise Tolerance and Survival Study						
Mean running time (seconds)[5]	988	-	-	389	-	-
Percent surviving to 357 days	67	-	-	22	-	-

1 Pulmonary capillary wedge pressure, change from baseline at 8 hours after treatment.
2 Change from baseline at 8 hours after treatment.
3 Percent improved after three weeks of therapy.
4 Percent improved after four weeks of therapy.
5 Running time measured after 80 days of therapy.

[a] Mitral regurgitation
[b] Dilated cardiomyopathy

HOW SUPPLIED: Each tablet strength is supplied in bottles containing 30 tablets (with desiccant).

STORAGE: PROTECT FROM MOISTURE. Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F). When not in use keep container tightly closed. Do not remove desiccant from the container. Subdivision of the product package is not recommended, as the product should be stored in an airtight container.

PLEASE FOLD THIS SHIPPING DOCUMENT IN HALF AND PLACE IT IN A WAYBILL POUCH AFFIXED TO YOUR SHIPMENT SO THAT THE BAR-CODE PORTION OF THE LABEL CAN BE READ AND SCANNED. ***WARNING: USE ONLY THE PRINTED ORIGINAL LABEL FOR SHIPPING. USING A PHOTOCOPY OF THIS LABEL FOR SHIPPING PURPOSES IS FRAUDULENT AND COULD RESULT IN ADDITIONAL BILLING CHARGES, ALONG WITH THE CANCELLATION OF YOUR FEDEX ACCOUNT NUMBER.

FROM: Mark Shepard (972)355-9700
Shotwell & Carr, Inc.
3535 Firewheel Drive
Suite A
Flower Mound, TX 750282628

SHIPPER'S FEDEX ACCOUNT NUMBER

FedEx
Federal Express

TO: FOOD & DRUG ADMINISTRATION (301)827-6880
Documents Management Branch
HFA-305, Room 4-62
5600 Fishers Lane

Rockville, MD 20857-

SHIP DATE: 02DEC99
MAN-WGT: 1 LBS

REF:

DELIVERY ADDRESS BARCODE (FEDEX-EDR)

CAD # 2526430 **PRIORITY OVERNIGHT** **FRI**
AA

TRK # 7907 9108 5147 **FORM 0201** **IAD** Deliver By: 03DEC99

20857-MD-US
DROP OFF

NJ EDGA